PHARMACOKINETICS OF MCLA-128 IN CYNOMOLGUS MONKEYS AND EXTRAPOLATION TO HUMAN TO SUPPORT SELECTION OF FIRST-IN-HUMAN DOSE

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Introduction

- MCLA-128 is a **bispecific humanized full length IgG1 monoclonal antibody** (mAb) with enhanced ADCC activity targeting receptor tyrosine kinases HER2 and HER3.
- MCLA-128 was designed using Merus' **CH3 technology**, to ensure efficient heterodimerisation and formation of a bispecific mAb. ADCC-enhancement was established using fucose glyco-engineering.
- MCLA-128 is developed to overcome **HER3-mediated resistance** to HER2 or EGFR targeted therapies.
- MAbs of the IgG1 subclass follow primarily **linear clearance** through cellular uptake followed by lysosomal degradation.[1]
- The pharmacokinetics (PK) of mAbs are characterized by **target mediated drug disposition** (TMDD), leading to saturation of the target and a co-existing nonlinear degradation.[1]

Objective

MCLA-128 was preclinically evaluated in cynomolgus monkeys to estimate PK parameters of MCLA-128 using a model based approach and to predict exposure to MCLA-128 in humans in order to support selection of first-in-human dose.

Data

PK data was obtained from two preclinical studies in cynomolgus monkeys:
- Single-dose toxicity study (n=6)
- First week of repeated dose toxicity study (n=32)

Methods

- MCLA-128 was quantified in serum using a validated electrochemiluminescence immunoassay.
- PK parameters were estimated using NONMEM (v.7.3) and parameters were scaled to humans using allometric scaling.
- Model evaluation, parameter estimate plausibility, parameter precision, visual predictive checks (VPC) and goodness of fit plots were evaluated.
- Safety margins for different proposed starting dose levels were obtained by dividing AUC in cynomolgus monkeys at the no observed adverse effect level (NOAEL), which was found at the highest dose evaluated (100 mg/kg), by the predicted AUC in human:

$$Safety\ Margin = \frac{Monkey\ AUC_{0\_\infty}}{Predicted\ Human\ AUC_{0\_\infty}}$$

- The percentage of receptor occupancy (RO) at maximum and average concentrations were calculated at each proposed dose level:

$$\%RO = 100 \cdot \frac{C_{max/average}}{K_m + C_{max/average}}$$

Model structure

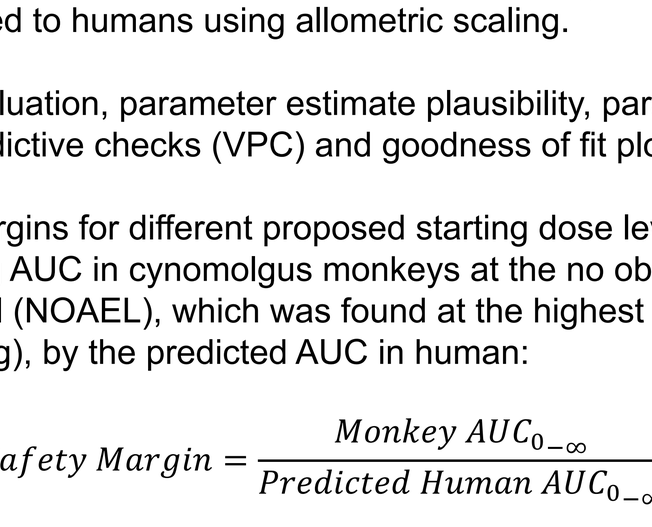

Figure 1: Model structure for the two-compartment PK model. V_1 = volume of distribution in the central compartment, V_2 = volume of distribution in the peripheral compartment, Q = distributional clearance, CL_L = linear clearance, CL_{NL} = nonlinear clearance, V_{max} = maximum velocity, K_M = drug concentration at which half of the drug-targets are occupied, [S] = concentration MCLA-128.

Results: Model building and parameter estimates

- The previously described PK model gave adequate fit of the data.
- Parameter estimates are depicted in Table 1.

Table 1: parameter estimates scaled to 70 kg human

Parameter	Estimate	RSE(%)	IIV	RSE(%)
CL (L/h)	0.0122	9.3	0.0172	13.1
V_1 (L)	3.18	2.8	0.0207	14.4
Q (L/h)	0.0312	6.6	-	-
V_2 (L)	3.59	14	-	-
K_m (mg/L)	0.273	65.2	1.19	109
V_{max} (mg/h)	0.527	13.1	-	-
RV_{prop} (sd)	0.106	10.1		
RV_{add} (sd)	0.039 FIX			

Results: Visual predictive checks

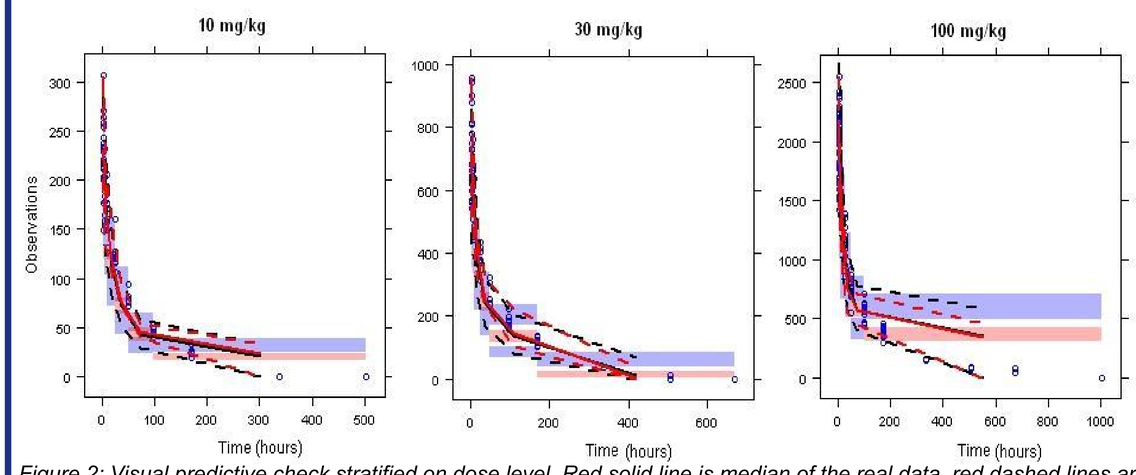

Figure 2: Visual predictive check stratified on dose level. Red solid line is median of the real data, red dashed lines are the percentiles of the real data. Black solid line is the median of the predicted data and the dashed black lines are the percentiles of the predicted data. Blue dots are the real data points. Shading blue and red areas are the approximated confidence interval of the predicted data.

Results: Safety margins

Table 2: Calculation of safety margins and percentage RO for different dose levels. MCLA-128 is administered as a flat dose, every three weeks.

Cohort	Flat dose (mg)	Dose Increase (%)	Assumed no. of patients	C_{max} %RO	C_{ave} %RO	Safety Margin #
1	10	-	1	91.5	15.6	6655
2	20	100	1	95.6	38.4	2010
3	40	100	1	97.7	67.0	623
4	80	100	1	98.9	86.2	203
5	160	100	1	99.4	94.9	68
6	240	50	3	99.6	97.3	36
7	360	50	3	99.7	98.6	19
8	480	33	3	99.8	99.1	11
9	600	25	3	99.9	99.4	7
10	750	25	3 or 6	99.9	99.6	4
11	900	20	3 or 6	99.9	99.7	3

Conclusions

- MCLA-128 shows coexisting linear and nonlinear clearance pathways in cynomolgus monkeys.
- MCLA-128 shows PK characteristics typical for IgG1 antibodies.[1]
- Both the CH3 technology and fucose glyco-engineering did not affect the PK characteristics of MCLA-128.
- Based on calculated safety margins the proposed first-in-human starting doses of 10 and 40 mg, administered every three weeks, have large safety margins.

References
[1]Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin. Pharmacokinet. 2010;49:633-59

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